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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/844,935	04/27/2001	Alexander Munishkin	Q01/08C	4219

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EXAMINER	
CHAKRABARTI, ARUN K	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 10/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/844,935	Muniskin
Examiner	**Art Unit**
Arun Chakrabarti	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Sep 2, 2003*.

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-8, 11, and 12* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-8, 11, and 12* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action*

DETAILED ACTION

Current status of the application

1. Applicant's remarks filed on September 2, 2003 have been entered. Claims 1-8, 11, and 12 are pending in this application.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1-8 are rejected under 35 U.S.C. 103(a) over Marsh et al.(Nucleic Acids Research, (1988), 16 (3), pages 981-995) in view of Spiegelman (U.S. Patent 3,444,043) (May 13, 1969) further in view of Holy et al. (U.S. Patent 5,977,061) (November 2, 1999).

Marsh et al. teaches a method of determining the presence or absence of a target molecule (abstract) comprising the steps of:

a) providing a first RNA molecule which can bind to a target molecule and has the formula:

5'-A-B-C-D-E-3'; (Figure 1, 2 and 4)

wherein A is a section of the RNA molecule having 10-10,000 nucleotides which section is, with another sequence, E, replicated by an RNA replicase, the letter "B" denotes a section of the RNA molecule having approximately 1 to 50000 nucleotides which section, with another sequence D, binds the target molecule under binding conditions, the letter "C" denotes a section of the RNA molecule having approximately 1 to 10000 nucleotides, the letter "D" denotes a section of the RNA molecule having approximately 1 to 50000 nucleotides which section, with another B, binds the target molecule under binding conditions, the section B and D, in combination, comprise in total at least 10 nucleotides, the first RNA molecule, with sections B and D bound to target, is acted upon by the RNA replicase to form a second RNA molecule, said second RNA molecule has the following formula:

5'-E'-X-A'-3';

wherein, E' is the complement to E, and A' is the complement to A, and the letter "X" denotes the complement of parts of the sections B and D which may be replicated, or the letter denotes the direct bond between sections E' and A', and second RNA molecule is replicated by the RNA replicase under replicating conditions and combining first RNA molecule with a sample (Figure 1, 2, 3 and 4 and Materials and Methods, page 983, lines 12-25);

b) imposing binding conditions on a sample potentially containing target molecules in the presence of first RNA molecule, in the presence of the target molecule, first RNA molecules forms a target-first RNA molecule complex to form a first modified sample (Figure 2, 3 and 4);

c) imposing RNA replicase reaction conditions on the first modified sample, in the presence of an RNA replicase, to form second RNA molecule in the presence of target to make a second modified sample (Materials and Methods, page 983, lines 12-25);

d) monitoring second modified sample for the presence of the second RNA molecule or its complement, which presence or absence is indicative of the presence or absence of the target molecule (Materials and Methods, page 983, lines 25-32 and Table 1).

Marsh et al. teaches that section "C" may serve as a non base-paired spacer to facilitate access of the replicase to the promoter (page 990, lines 9-10).

Marsh et al. does not teach a composition by providing paired RNA molecules.

Marsh et al does not teach section "C" of the RNA molecule which section is capable of preventing the replication of the first molecule by the RNA replicase (abstract and column 7, lines 8-44).

Spiegelman teaches the customized preparation of RNA templates as he states, "An RNA template of an in vitro replicating system may be formed in situ. If one were, for example, to introduce foreign bases or nucleotides (e.g., analogues of known bases or nucleotides) into the replicating system, a mutant may be formed which would be the biologically active template for replication with those same bases or nucleotides, in such instances, one would be synthesizing mutants in vitro in a known way (Column 5, lines 1-8)".

Spiegelman teaches section "C" of the RNA molecule which section is capable preventing the replication of the first molecule by the RNA replicase (abstract and column 7, lines 8-44).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to substitute RNA template model of Spiegelman as the identification of target molecule in the method of Marsh et al., since Spiegelman et al. states "There is good evidence that the replicase recognizes the particular sequence of nucleotides at the beginning and at the end of the biologically active viral RNA template during the course of the replication. It is inferred from this recognition pattern that the intermediate portion of the RNA template is not essential to the direction of or instruction found in the replication mechanism studied. This suggests that the recognition sequences of nucleotides present at the beginning and end of a biologically active RNA template molecule can be selectively bonded to otherwise non-biologically active or non-viral RNA to produce a synthesized biologically active RNA product. It is thought that the RNA forms a circle and these two recognition sequences of the molecule overlap each other to provide double-stranded regions: such overlapped regions could afford,

therefore, identification of the RNA molecule in a single, rapid scanning process (Column 4, lines 59-75)". An ordinary practitioner would have been motivated to combine the model of custom made RNA template of Spiegelman into the method of Marsh et al. in order to achieve the express advantages noted by Spiegelman of a method which can provide identification of the RNA molecule in a single, rapid scanning process.

Marsh et al. in view of Spiegelman do not teach the nucleic acid, wherein the target is a small or large organic molecule such as a peptide, protein, and derivatives thereof, although Spiegelman suggests analogues of known bases or nucleotides may be incorporated in the RNA molecule at suitable positions.

Holy et al teaches the nucleic acid, wherein the target is a small or large organic molecule such as a peptide, protein, and derivatives thereof , which can be attached to the analogues of known bases or nucleotides (Column 12, line 49 to Column 13, line 2).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the nucleic acid, wherein the target is a small or large organic molecule such as a peptide, protein, and derivatives thereof , which can be attached to the analogues of known bases or nucleotides of Holy et al as the identification of target molecule in the method of Marsh et al in view of Spiegelman et al. since Holy et al. states "In one embodiment of this alternative, antibodies are raised against the compounds of this invention. Such antibodies bind to the analogue of this invention and thereby are useful in detecting its presence as label for a protein or oligonucleotide (Column 12, line 64 to Column 13, line 2)". An

ordinary practitioner would have been motivated to combine and substitute the nucleic acid, wherein the target is a small or large organic molecule such as a peptide, protein, and derivatives thereof , which can be attached to the analogues of known bases or nucleotides of Holy et al as the identification of target molecule in the method of Marsh et al in view of Spiegelman et al. in order to achieve the express advantages, as noted by Holy et al., of nucleotide analogue which are useful in detecting its presence as label for a protein.

4. Claims 11 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Marsh et al.(Nucleic Acids Research, (1988), 16 (3), pages 981-995) in view of Spiegelman (U.S. Patent 3,444,043) (May 13, 1969) further in view of Holy et al. (U.S. Patent 5,977,061) (November 2, 1999) further in view of Stratagene Catalog (1988, Page 39).

Marsh et al. in view of Spiegelman further in view of Holy et al. teach the compositions of claims 1-8 as described above in detail.

Marsh et al. in view of Spiegelman further in view of Holy et al. do not teach the motivation to combine all the reagents for detecting an analyte in a sample in the form of a kit.

Stratagene catalog teaches a motivation to combine reagents into kit format (page 39).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the compositions of claims 1-8 of Marsh et al. in view of Spiegelman further in view of Holy et al. into a kit format as discussed by Stratagene catalog since the Stratagene catalog teaches a motivation for combining reagents of use in an assay into a kit, "Each kit provides two services: 1) a variety of different reagents have been assembled and

pre-mixed specifically for a defined set of experiments. Thus one need not purchase gram quantities of 10 different reagents, each of which is needed in only microgram amounts, when beginning a series of experiments. When one considers all of the unused chemicals that typically accumulate in weighing rooms, desiccators, and freezers, one quickly realizes that it is actually far more expensive for a small number of users to prepare most buffer solutions from the basic reagents. Stratagene provides only the quantities you will actually need, premixed and tested. In actuality, the kit format saves money and resources for everyone by dramatically reducing waste. 2) The other service provided in a kit is quality control (page 39, column 1).

Response to Amendment

5. In response to amendment, 112(second paragraph) rejections have been withdrawn. However, previous 103(a) rejections have been maintained properly.

Response to Arguments

6. Applicant's arguments with respect to all pending claims have been considered but are not persuasive.

In response to applicant's arguments against the references individually (page 9, last paragraph to page 12, second paragraph), one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re*

Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument (page 10, second and third paragraph, page 11, first paragraph, and fourth paragraph, and page 12, second paragraph, and page 13, second paragraph) that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., (a) Section "C" comprises stop sequence, (b) a target protein molecule has to bind with sections "B" and "D" of the first molecule, then replicase activity takes place, c) Section "C" comprises stop sequence that is contiguous with the larger RNA molecule, (d) the ligand is an RNA molecule, (e) If the target protein is present, then the first RNA will interact and bind thereto. Once bound, the first RNA molecule can serve as a template for the synthesis of a second RNA molecule. The production of the second RNA molecule then serves as a signal amplification event. If, however, the target protein is absent from the sample, then, the first RNA will not serve as a template for RNA synthesis) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant also argues (page 8, third paragraph and page 13, fourth paragraph) that there is no motivation to combine the references. This argument is not persuasive, especially in the presence of strong motivation provided by Holy et al. since Holy et al. states "In one embodiment of this alternative, antibodies are raised against the compounds of this invention. Such antibodies

bind to the analogue of this invention and thereby are useful in detecting its presence as label for a protein or oligonucleotide (Column 12, line 64 to Column 13, line 2)". Similar logic is applicable to other combinatory references.

Applicant then argues (page 8, third paragraph and page 13, fourth paragraph) that the 103 rejections are improper because it lacks a reasonable expectation of success.

With regard to the "lacks a reasonable expectation of success" argument, The MPEP 2143.02 states , "Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. In re Rinehart , 531 F.2d 1048, 189 USPQ 143 (CCPA 1976) (Claims directed to a method for the commercial scale production of polyesters in the presence of a solvent at superatmospheric pressure were rejected as obvious over a reference which taught the claimed method at atmospheric pressure in view of a reference which taught the claimed process except for the presence of a solvent. The court reversed, finding there was no reasonable expectation that a process combining the prior art steps could be successfully scaled up in view of unchallenged evidence showing that the prior art processes individually could not be commercially scaled up successfully.). See also Amgen, Inc. v. Chugai Pharmaceutical Co ., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir.), cert. denied , 502 U.S. 856 (1991) (In the context of a biotechnology case, testimony supported the conclusion that the references did not show that there was a reasonable expectation of success. 18 USPQ2d at 1022, 1023.); In re O'Farrell , 853 F.2d 894, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988) (The court held the claimed method would

have been obvious over the prior art relied upon because one reference contained a detailed enabling methodology, a suggestion to modify the prior art to produce the claimed invention, and evidence suggesting the modification would be successful.)."

There is no evidence of record submitted by applicant demonstrating the absence of a reasonable expectation of success. There is evidence in the Holy et al. reference of the enabling methodology, the suggestion to modify the prior art, and evidence that a number of different small or large organic molecule such as a peptide, protein, and derivatives thereof , were attached to the analogues of known bases or nucleotides (Column 12, line 49 to Column 13, line 2). This evidence of functionality trumps the attorney arguments, which argues that Holy reference is an invitation to research, since Holy steps beyond research and shows the functional product.

In view of the response to arguments, all previous 103(a) rejections are hereby properly maintained.

Conclusion

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D. whose telephone number is (703) 306-5818.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119.Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Chantae Dessau whose telephone number is (703) 605-1237. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission via the P.T.O. Fax Center located In Crystal Mall 1. The CM1 Fax Center numbers for Technology Center 1600 are either (703) 305-3014 or (703) 308-4242. Please note that the faxing of such papers must conform with the Notice to Comply published In the Official Gazette, 1096 OG 30 (November 15, 1989).

Arun Kr. Chakrabarti

ARUN K. CHAKRABARTI
PATENT EXAMINER

Arun Chakrabarti

Patent Examiner

Art Unit 1634,

October 9, 2003

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